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Cigarette Smoking and Pancreas Cancer: a Case–Control Study Based on Direct Interviews

*Debra T. Silverman, Janet A. Dunn, Robert N. Hoover, Mark Schiffman, Keith D. Lillemoe, Janet B. Schoenberg, Linda M. Brown, Raymond S. Greenberg, Richard B. Hayes, G. Marie Swanson, Sholom Wacholder, Ann G. Schwartz, Jonathan M. Liff, Linda M. Pottern**

Background: **Cigarette smoking is the most consistently reported risk factor for pancreas cancer, yet the dose–response relationship in many pancreas cancer studies is weak. Because of the poor prognosis for pancreas cancer, many case–control studies have been based largely on interviews with proxy respondents, who are known to report less reliable information on detailed smoking habits than original subjects.** ***Purpose:*** **Our purpose was to evaluate cigarette smoking as a risk factor for pancreas cancer based on data obtained only from direct interviews and to estimate the effects of quitting smoking and of switching from nonfiltered to filtered cigarettes on risk. Our objective also was to estimate the contribution of cigarette smoking toward explaining the higher pancreas cancer incidence experienced by black Americans compared with white Americans.** ***Methods:*** **A population-based, case–control study of pancreas cancer was conducted during 1986-1989 in Atlanta, Ga., Detroit, Mich., and 10 counties in New Jersey. Direct interviews were successfully completed with 526 case patients and 2153 control subjects aged 30-79 years, making this the largest population-based, case–control study of pancreas cancer to date based only on direct interviews.** ***Results:*** **Cigarette smokers had a significant, 70% increased risk of pancreas cancer compared with the risk in nonsmokers. A significant, positive trend in risk with increasing duration smoked was apparent ($P<.0001$), with long-term (≥40 years) smokers experiencing a modest 2.1-fold risk. We also observed a negative trend in risk with increasing years quit smoking. Smokers who quit for more than 10 years experienced about a 30% reduction in risk relative to current smokers; quitters of 10 years or less experienced no risk reduction. Switching from nonfiltered to filtered cigarettes did not appear to decrease risk. Compared with nonsmokers, subjects who smoked only filtered cigarettes had a 50% elevated risk and those who smoked only nonfiltered cigarettes had a 40% elevated risk. The proportion of pancreas cancer attributable to cigarette smoking was 29% in blacks and 26% in whites.** ***Conclusions:*** **The relationship between cigarette smoking and pancreas cancer risk is likely to be causal, despite the weakness of the dose–response data. Long-term smoking cessation clearly reduces risk, whereas switching from nonfiltered to filtered cigarettes may not be beneficial. Cigarette smoking appears to explain little of the excess pancreas cancer risk experienced by blacks.** ***Implications:*** **Elimination of cigarette smoking would eventually prevent approximately 27% of pancreas cancer, saving 6750 lives in the United States annually. [J Natl Cancer Inst 86:1510-1516, 1994]**

Cancer of the pancreas is the fifth leading cause of death from cancer in the United States, with 25 000 deaths from pancreas cancer expected to have occurred in 1993 (*1*). The incidence of

**Affiliations of authors:* D. T. Silverman, R. N. Hoover, M. Schiffman, L. M. Brown, R. B. Hayes, S. Wacholder, L. M. Pottern, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Md.

J. A. Dunn, Cancer Research Campaign Trials Unit, University of Birmingham, Edgbaston, England.

K. D. Lillemoe, Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Md.

J. B. Schoenberg, Special Epidemiology Program, New Jersey State Department of Health, Trenton.

R. S. Greenberg, J. M. Liff, Division of Epidemiology, Emory University School of Public Health, Atlanta, Ga.

G. M. Swanson, College of Human Medicine, Michigan State University, East Lansing.

A. G. Schwartz, Department of Clinical Epidemiology and Family Medicine, University of Pittsburgh School of Medicine, Pa.

Correspondence to: Debra T. Silverman, Sc.D., National Institutes of Health, Executive Plaza North, Rm. 415, Bethesda, MD 20892.

See "Notes" section following "References."

pancreas cancer in the United States is about 50% higher in blacks than in whites (*2*). The etiology of pancreas cancer is poorly understood. Cigarette smoking is the most consistently reported risk factor (*3*), yet the dose–response relationship in many studies of pancreas cancer is weak (*4-18*). Because of the unfavorable survival associated with this disease, many case–control studies have been based largely on interviews with proxy respondents (*10,11,13,15-20*), who are known to report less reliable information on detailed smoking habits than original subjects. The effect that misclassification of smoking habits by proxy respondents has on quantifying the dose–response relationship is unclear. Most large case–control studies have included too few direct interviews to compare the dose–response relationship based on proxy and direct respondents.

The present study is the largest population-based, case–control study of pancreas cancer to include only direct interviews. Our purpose was to examine cigarette smoking as a risk factor for pancreas cancer. We quantified the dose–response relationship and estimated the effects of quitting smoking and of switching from nonfiltered to filtered cigarettes on risk of developing pancreas cancer. We also estimated the extent to which cigarette smoking may explain the excess risk of pancreas cancer experienced by blacks.

Subjects and Methods

We conducted a population-based, case–control study of malignancies (i.e., pancreas, esophagus, and prostate cancers and multiple myeloma) that occur excessively in blacks. One general population control group provided controls for four cancer types.

The case series in this analysis consisted of all cases of carcinoma of the pancreas (International Classification of Diseases for Oncology[1] code = 157) first diagnosed from August 1986 through April 1989 among residents aged 30-79 years from three geographic areas, i.e., Atlanta, Ga. (DeKalb and Fulton counties), Detroit, Mich. (Macomb, Oakland, and Wayne counties), and the state of New Jersey (10 counties). All cases of pancreas cancer, regardless of the presence of tissue confirmation, were initially included to ensure both the population-based nature of the case series and completeness of case ascertainment. Because about 15% of the cases lacked tissue confirmation, in-depth medical chart reviews were conducted by a physician–epidemiologist and a surgeon specializing in pancreas cancer to determine the accuracy of diagnosis. Patients were considered "unlikely" to have pancreas cancer if they did not satisfy one of the following criteria: 1) A pancreatic mass was known by radiographic visualization or surgery, with a compatible histologic diagnosis; 2) a pancreatic mass was known by surgery and, although a biopsy specimen was not obtained, it clearly appeared to be malignant due to either visible hepatic metastases or local extension; or 3) a pancreatic mass was known by radiographic visualization, although a biopsy specimen was not obtained, and there were supporting clinical signs, symptoms, and course (e.g., rapid death). Overall, only 5.5% of identified case patients were considered unlikely to have had pancreas cancer were excluded from all analyses.

We identified 1153 case patients and interviewed 526 (46%) of them. The primary reason for no response was death because of the poor prognosis of patients diagnosed with this tumor. Four hundred seventy-one case patients had died before the interview could be conducted, despite the emphasis on identifying and interviewing case patients within 6 weeks of diagnosis. The median length of time from diagnosis to interview was 7 weeks. The remaining 156 case patients were not interviewed because of illness (n = 89), physician or patient refusal (n = 51), or language or other problems (n = 16).

The control series was randomly selected from the general population; the control subjects were frequency matched to the area–age–race–sex distribution of patients with all four types of cancer combined. The age matching was done within 5-year age groups. Control subjects aged 30-64 years were selected from 17 746 households by random-digit dialing (*21*). Eighty-six percent of these households provided a household census that served as the basis for a sampling frame for selection of younger control subjects. Of the 1568 control subjects selected from these households, we interviewed 1227 (78%). The remaining 341 control subjects were not interviewed because of death (n = 5), illness (n = 23), refusal to participate (n = 258), or language or other problems (n = 55).

Control subjects aged 65-79 years were drawn by stratified random sampling from the rosters of the Health Care Financing Administration (Baltimore, Md.) of the population older than age 64 years in each study area. Of the 1232 older control subjects selected, we interviewed 926 (75%). The remaining 306 older control subjects were not interviewed because of death (n = 22), illness (n = 63), refusal to participate (n = 177), or language or other problems (n = 44).

The numbers of interviewed case patients and control subjects by geographic area and race were as follows: Atlanta whites, 38 case patients and 257 control subjects; Atlanta blacks, 42 case patients and 196 control subjects; Detroit whites, 118 case patients and 449 control subjects; Detroit blacks, 72 case patients and 420 control subjects; New Jersey whites, 157 case patients and 473 control subjects; and New Jersey blacks, 65 case patients and 351 control subjects.

Subjects were usually interviewed at home by interviewers who were not informed of either the case or control status of the subject or the hypotheses under study. Prior to interview, written informed consent to participate in the study was obtained from each subject. The questionnaire was designed to elicit detailed information on smoking habits, alcohol consumption, coffee and tea drinking, dietary factors, medical conditions, usual occupation, family history of cancer, and socioeconomic status.

Cigarette smokers were defined as subjects who reported smoking at least one cigarette per day for 6 months or longer. They were asked detailed questions about their smoking habits, including age at which they started and stopped smoking, number of years and usual amount smoked, and depth of inhalation. These data were also collected separately for smokers of filtered and nonfiltered cigarettes.

The effects of smoking habits on pancreas cancer risk were quantified by the odds ratio (OR). ORs and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis (*22,23*). Models included terms for cigarette smoking, age at diagnosis/interview, race, sex, and study area as well as terms for potential confounders (i.e., alcohol consumption, gallbladder disease, and income). Additional adjustments for diabetes mellitus, pancreatitis, allergies, family history of pancreas cancer, and dietary risk factors (i.e., vegetable and simple/complex carbohydrate consumption) had little or no impact on point estimates and were not included in the final models, unless otherwise specified. A number of other suspected risk factors, such as coffee drinking and gastrectomy, were not adjusted for because they were not associated with risk in our data. To test for trend, we treated the exposure variable as continuous in the model by entering the median value for each level of the categorical variable among the control subjects. Population-attributable risks (PARs) were computed by the method of Whittemore (*24*) and were adjusted for race, sex, geographic area, and age. Two-sided 95% CIs for the adjusted PAR were also calculated according to the method of Whittemore (*24*).

Interviewed subjects were excluded from analysis for the following reasons: presence of pancreas cancer was unlikely (16 case patients), presence of islet cell carcinoma (10 case patients), no medical record available for review (six case patients), unsatisfactory interview (one case patient and seven control subjects), and missing data (12 case patients and 11 control subjects). The smoking analysis was based on first-person interviews with 481 likely case patients with a diagnosis of exocrine pancreas cancer and 2135 population control subjects.

Results

Because of the high mortality and resulting low response rate in the case patient series, we were concerned about the representativeness of the case patient series with regard to exposures under study. To determine the comparability of those who died and those who lived long enough to be interviewed, we conducted interviews with next of kin of a sample of case patients who died; thus, we interviewed next of kin of 210 white and 115 black deceased case patients. The next-of-kin interview was

limited to broad questions that next-of-kin respondents have been shown to answer reliably (25). The overall percentage of case patients who ever smoked cigarettes was similar among directly interviewed case patients and among that reported by next of kin (69% and 64%, respectively), which suggests that interviewed case patients were probably representative of the total case patient series with respect to smoking status.

Effect of Cigarette Smoking Status and Dose on Risk

Cigarette smokers experienced a significant, 70% increased risk of pancreas cancer compared with nonsmokers (Table 1). The OR for current smokers was 2.0 (95% CI = 1.5-2.6), in contrast to an OR of 1.4 (95% CI = 1.1-1.9) for those who quit smoking more than 2 years prior to interview.

Table 1 shows pancreas cancer risk estimated by three measures of dose: number of cigarettes smoked per day, duration smoked, and pack-years smoked. A significant trend in risk with increasing dose was apparent for each of these measures, although the trend was consistent for only duration and pack-years smoked. The positive trends by duration and pack-years smoked also were consistent when the data were stratified by age at diagnosis/interview (i.e., 50-59 years, 60-69 years, and 70-79 years). Compared with nonsmokers, subjects who smoked for at least 40 years had an OR of 2.1 (95% CI = 1.6-2.9) and those who smoked at least 45 pack-years had an OR of 2.2 (95% CI = 1.6-3.1). Estimates of risk for duration and pack-years smoked were almost identical, indicating that duration smoked captured most of the overall dose effect. Consequently, duration smoked will be used to express dose effect in all subsequent tables.

We also estimated risk simultaneously by amount and duration smoked (data not shown). Within each level of amount smoked, a consistent trend in risk with increasing duration was apparent. In contrast, the trend in risk with increasing amount smoked was consistent only among long-duration smokers. Among subjects who smoked at least 40 years, ORs (relative to nonsmokers) by amount smoked were 1.4 (95% CI = 0.9-2.2) for fewer than 20 cigarettes smoked per day, 2.5 (95% CI = 1.7-3.5) for 20-39 cigarettes smoked per day, and 3.4 (95% CI = 2.0-5.8) for 40 or more cigarettes smoked per day.

Effect of Smoking by Sex and Race on Risk

The effect of smoking by sex and by race is presented in Table 2. Men experience a 50% higher incidence of pancreas cancer than women (2). Although both men and women experienced increased risk with increasing duration smoked, women had higher estimates of relative risk than men, among smokers of 20-39 years and 40 or more years. The interaction between sex and duration smoked was statistically significant (P = .03). Cigarette smoking accounted for 26% (95% CI = 12%-48%) of pancreas cancer in men and 29% (95% CI = 18%-42%) of pancreas cancer in women. Although a higher proportion of men than women "ever" smoked cigarettes (69% and 46%, respectively), smoking did not explain the higher risk of pancreas cancer in men.

Table 1. Number of case patients and control subjects and ORs for pancreas cancer according to various measures of cigarette exposure: base line is nonsmokers

Cigarette smoking status	No. of cases	No. of controls	OR*	95% CI
Never smoked	149	840	1.0	
Ever smoked†	332	1295	1.7	1.3-2.2
Former smokers	133	626	1.4	1.1-1.9
Current smokers‡	197	668	2.0	1.5-2.6
Cigarettes smoked per day				
<20	99	522	1.3	0.9-1.7
20-39	178	584	2.2	1.7-3.0
≥40	54	186	1.8	1.2-2.8
			P<.0001§	
Duration smoked, y				
<20	41	263	1.1	0.7-1.6
20-39	151	550	1.8	1.3-2.4
≥40	138	449	2.1	1.6-2.9
			P<.0001§	
Pack-years‖ smoked				
<20	80	446	1.3	0.9-1.7
20-44	131	455	1.9	1.4-2.6
≥45	118	360	2.2	1.6-3.1
			P<.0001§	

*ORs adjusted for age, race, sex, area, income, alcohol consumption, and gallbladder disease.

†Includes two case patients and one control subject with missing information on current/former status.

‡Includes former smokers who quit within the immediate 2 years prior to interview.

§P value for test of linear trend.

‖Pack-years = usual packs smoked per day × duration smoked in years.

Table 2. Number of case patients and control subjects and ORs for pancreas cancer according to duration smoked cigarettes by sex and race; base line is nonsmokers

	Years smoked				
Study subjects	0	<20	20-39	≥40	P for trend
Sex					
Men					
No. of cases	53	28	88	75	
No. of controls	418	174	399	337	
OR*,†	1.0	1.4	1.6	1.7	.009
95% CI		0.8-2.3	1.1-2.4	1.1-2.7	
Women					
No. of cases	96	13	63	63	
No. of controls	422	89	151	112	
OR*,‡	1.0	0.7	2.0	2.8	<.0001
95% CI		0.3-1.3	1.3-3.0	1.8-4.3	
Race					
White					
No. of cases	90	29	110	77	
No. of controls	450	177	321	205	
OR§	1.0	1.1	2.2	2.3	<.0001
95% CI		0.7-1.8	1.5-3.1	1.5-3.4	
Black					
No. of cases	59	12	41	61	
No. of controls	390	86	229	244	
OR§	1.0	1.1	1.3	2.2	.003
95% CI		0.5-2.4	0.8-2.1	1.3-3.5	

*ORs adjusted for age, race, area, alcohol consumption, and gallbladder disease.

†ORs also adjusted for income.

‡ORs also adjusted for simple carbohydrate consumption.

§ORs adjusted for age, sex, area, income, alcohol consumption, and gallbladder disease.

To determine whether a part of the excess in pancreas cancer risk experienced by blacks might be attributable to smoking, we examined risk by race. Relative risk estimates for blacks and whites were almost identical at each level of duration smoked, except for the 20- to 39-year category, where the risk for whites was higher than that for blacks (OR = 2.2 and 1.3, respectively). The prevalence of ever smokers among blacks and whites was also similar. The proportion of black and white population control subjects who had ever smoked was 0.60 and 0.62, respectively, and the proportion of black and white control subjects who smoked for 20 years or more was 0.50 and 0.46, respectively. The proportion of pancreas cancer attributable to cigarette smoking was 27% (95% CI = 17%-40%) in the total study group, 29% (95% CI = 15%-49%) in blacks, and 26% (95% CI = 14%-43%) in whites, suggesting that cigarette smoking explains little of the excess in pancreas cancer risk experienced by blacks.

Effect of Smoking Cessation on Risk

Table 3 shows the effect of time since quitting smoking on pancreas cancer risk. Because amount smoked did not confound the relationship between risk and years quit, amount smoked was not included in the model and estimates of risk were relative to risk among nonsmokers. Risk was particularly high for those who quit within 2 years prior to diagnosis, suggesting that some case patients may have had early symptoms that caused them to stop smoking. For this reason, former smokers who quit within 2 years of diagnosis were included with current smokers throughout these analyses.

Subjects who stopped smoking more than 10 years before the diagnosis/interview experienced about a 30% reduction in risk relative to current smokers. Cessation of smoking for 10 years or less did not appear to reduce risk. It was not possible to determine if the beneficial effect of long time since quitting was attributable to shorter total duration smoked; years quit and duration were highly correlated ($r = .6$), and the effects of these two factors could not be separated while simultaneously adjusting for age at diagnosis/interview (*26*).

Smokers who quit for more than 20 years experienced a 30% higher risk of pancreas cancer than nonsmokers. Because there were too few former smokers who quit for more than 30 years to estimate risk, we could not determine whether risk eventually drops to the level of nonsmokers.

Table 3. Number of case patients and control subjects and ORs for pancreas cancer according to time since quitting smoking; base line is nonsmokers

Years since quitting	No. of cases	No. of controls	OR*	95% CI
Nonsmoker	149	840	1.0	
0 (current smokers)	158	590	1.8	1.4-2.4
1-2	39	78	3.1	2.0-5.0
3-5	21	69	2.0	1.1-3.5
6-10	30	118	1.8	1.1-2.9
11-20	34	190	1.2	0.8-1.9
>20	48	249	1.3	0.8-1.9

*ORs adjusted for age, race, sex, area, income, alcohol consumption, and gallbladder disease.

Effect of Cigarette Filtration on Risk

We examined the risk associated with use of filtered and nonfiltered cigarettes. Relative to nonsmokers, the OR for subjects who exclusively smoked filtered cigarettes (OR = 1.5; 95% CI = 1.1-2.1) was almost identical to that for those who exclusively smoked nonfiltered cigarettes (OR = 1.4; 95% CI = 1.0-2.1). Subjects who switched from nonfiltered to filtered cigarettes experienced a greater risk (OR = 1.9; 95% CI = 1.4-2.6) than those who smoked only one type of cigarette. Subjects who switched, however, tended to have longer total durations smoked.

Table 4 shows ORs estimated by duration of use of both filtered and nonfiltered cigarettes among current smokers only. Within each level of duration, the effect of smoking filtered cigarettes appeared to be similar to that of smoking nonfiltered cigarettes. Risk from smoking each type of cigarette tended to increase with increasing duration of smoking that type of cigarette, holding duration of the other type constant.

Effect of Inhalation of Cigarette Smoke on Risk

We also estimated risk by depth of inhalation of filtered and nonfiltered cigarettes. For smokers of filtered cigarettes, ORs were 1.0 for inhalation into the mouth only (base line), 0.7 (95% CI = 0.5-1.2) for inhalation into the mouth and throat, and 1.1 (95% CI = 0.7-1.7) for inhalation into the chest. For smokers of nonfiltered cigarettes, ORs were 1.0 for inhalation into the mouth only (base line), 0.9 (95% CI = 0.5-1.5) for inhalation into the mouth and throat, and 1.3 (95% CI = 0.8-2.1) for inhalation into the chest. Reported depth of inhalation of both filtered and nonfiltered cigarettes did not appear to be related to pancreas cancer risk.

Time Period of Exposure

It has been suggested that the weakness of the dose–response relationship seen in many epidemiologic studies of cigarette smoking and pancreas cancer may be related to the focus on lifetime smoking habits when the only relevant time period of exposure may be smoking within 10-15 years of diagnosis/interview (*20*). To test this hypothesis, we estimated risk by total duration smoked, cross-classified by duration smoked within 10 years of diagnosis/interview (Table 5). Within each level of total duration, risk tended to increase with increasing duration smoked within 10 years of diagnosis/interview, but this trend was not consistent. In fact, for subjects who smoked a total of 40 years or more, duration smoked within 10 years of diagnosis/interview seemed only weakly related to risk. When both total duration and duration smoked within 10 years of diagnosis/interview were included in the model, ORs for duration smoked within 10 years of diagnosis/interview were 1.0 for 0 years (base line), 1.1 (95% CI = 0.6-1.9) for less than 5 years, 1.2 (95% CI = 0.6-2.2) for 5-7 years, and 1.2 (95% CI = 0.8-1.9) for 8-10 years. These estimates reflected a small increment in risk contributed by duration smoked within 10 years of diagnosis/interview after the effect of total duration was taken into account.

On the other hand, for each level of duration smoked within 10 years of diagnosis/interview, risk generally increased with increasing total duration smoked. Subjects who stopped smoking

Table 4. ORs for pancreas cancer according to duration of use of filtered and nonfiltered cigarettes among current smokers only

Duration of use of filtered cigarettes	Duration of use of nonfiltered cigarettes			
	None	1-10 y	11-20 y	>20 y
None				
OR (95% CI)	—	1.7 (0.5-5.6)	2.5 (0.7-8.5)	2.5 (0.9-7.1)
No. of cases/No. of controls	—	11/60	9/45	48/210
1-10 y				
OR (95% CI)	1.0* (—)	1.7 (0.5-6.5)	0.5 (0.1-3.2)	2.4 (0.8-7.9)
No. of cases/No. of controls	6/43	6/44	2/36	13/59
11-20 y				
OR (95% CI)	2.0 (0.6-6.4)	2.4 (0.8-7.5)	4.8 (1.6-14.5)	4.0 (1.3-12.2)
No. of cases/No. of controls	12/63	12/66	22/48	19/61
>20 y				
OR (95% CI)	2.7 (1.0-7.4)	3.5 (1.3-9.5)	3.5 (1.2-10.2)	2.9 (0.8-10.2)
No. of cases/ No. of controls	51/182	58/168	30/95	8/30

*Base-line category is 1-10 years of filtered cigarette use, never smoked nonfiltered cigarettes. ORs adjusted for age, race, sex, area, income, alcohol consumption, and gallbladder disease.

Table 5. ORs for pancreas cancer according to total duration of cigarette smoking and duration of smoking within 10 years of diagnosis/interview among cigarette smokers only

Total duration	Duration smoked within 10 y prior to diagnosis/interview			
	0 y*	<5 y	5-7 y	8-10 y
<20 y				
OR (95% CI)	1.0† (—)	0.7 (0.1-3.4)	NE‡	1.7 (0.7-4.4)
No. of cases/No. of controls	31/200	2/19	0/11	8/33
20-39 y				
OR (95% CI)	1.5 (0.9-2.7)	1.5 (0.7-3.3)	2.5 (1.0-6.2)	1.9 (1.1-3.2)
No. of cases/No. of controls	44/191	14/62	10/27	83/270
≥40 y				
OR (95% CI)	1.7 (0.7-4.6)	2.4 (1.1-5.5)	1.9 (0.8-4.5)	2.2 (1.4-3.6)
No. of cases/No. of controls	7/35	13/38	11/34	107/342

*Subjects who stopped smoking more than 10 years before diagnosis/interview had 0 years' duration within 10 years prior to diagnosis/interview.
†Base-line category is <20 years' total duration and 0 years' duration within 10 years prior to diagnosis/interview. ORs adjusted for age, race, sex, area, income, alcohol consumption, and gallbladder disease.
‡OR could not be estimated because of small numbers (0 case patients and 11 control subjects).

more than 10 years prior to diagnosis/interview and, thus, had "0" duration smoked within 10 years of diagnosis/interview experienced a 50%-70% increased risk with increasing total duration. ORs for total duration smoked when duration smoked within 10 years of diagnosis/interview was included in the model were 1.0 for less than 20 years (base line), 1.6 (95% CI = 1.0-2.4) for 20-39 years, and 1.8 (95% CI = 1.1-3.2) for 40 or more years. These estimates represented the effect of duration smoked more than 10 years prior to diagnosis/interview. Thus, although duration smoked within 10 years of diagnosis/interview appeared to contribute independently to risk, it was not the only determinant of risk; duration smoked more than 10 years prior to diagnosis/interview contributed to risk as well.

Discussion

Cigarette smoking has been associated with increased risk of pancreas cancer in at least 29 epidemiologic studies (*3,10,11,13,15-20,27-31*). The dose–response relationship observed in these studies, however, was frequently weak.

Our results also indicate that cigarette smoking is associated with increased risk of pancreas cancer. The overall OR was 1.7 (95% CI = 1.3-2.2), with risk reaching 2.1 (95% CI = 1.6-2.9) for subjects who smoked for at least 40 years. Although the positive trends in risk with duration and pack-years smoked were both statistically significant and consistent, the relatively small excess risk experienced by long-duration smokers may suggest that cigarette smoke either is a weak to moderate pancreatic carcinogen or is not causally related to risk.

Alternatively, biased recall of smoking habits by critically ill case patients may have resulted in dilution of estimates of smoking risk, just as misclassification of smoking habits may have weakened the dose–response relationship reported in studies based largely on proxy respondents (*10,11,13,15,16,18*). In a methodologic study, however, Lyon et al. (*32*) found that the dose–response relationship was only minimally attenuated when ORs were based on proxy data. Results of cohort studies (*4-6,33,34*), which are not susceptible to differential recall bias, suggested that the dose–response relationship was fairly weak, supporting the hypothesis that either cigarette smoking is not a

strong risk factor or the relationship is noncausal. The latter seems unlikely, however, because the association with cigarette smoking has been consistently observed in almost all studies of pancreas cancer, regardless of study design, study population, or the period of study. Cessation of smoking appeared to reduce pancreas cancer risk, further supporting a causal association. In addition, pancreatic tumors have been induced experimentally in rodents by administration of tobacco-specific nitrosamines (*35,36*), providing evidence of biologic plausibility.

Howe et al. (*20*) proposed that the observed weakness in the dose–response relationship may be related to timing of exposure, where the relevant exposure was cigarette consumption in the 10- to 15-year period immediately prior to diagnosis/interview rather than lifetime cigarette consumption. In a case–control study of pancreas cancer based largely on proxy respondents in Toronto, Canada, the dose–response relationship did become stronger when exposure was restricted to smoking habits in the 15 years immediately preceding diagnosis/interview. Our data only partly support this hypothesis, however. We found that duration smoked within 10 years of diagnosis/interview had a small, independent effect on risk, but it was not the sole determinant of risk. We also found that total duration, including duration smoked more than 10 years prior to diagnosis/interview, was an important determinant of risk. One possible explanation for the stronger dose–response relationship reported by Howe et al. (*20*) in the recent time period may be that proxy respondents report recent smoking habits more accurately than they report usual lifetime habits.

The present study is the first to examine the dose–response relationship by race based on large numbers of black and white subjects. Our results indicate that both the magnitude of pancreas cancer risk associated with cigarette smoking and the prevalence of smoking are similar in blacks and whites. Thus, cigarette smoking appears to explain little of the observed excess in pancreas cancer risk experienced by blacks. This excess, however, may be due to other putative risk factors, such as alcohol consumption, and/or racial differences in genetic susceptibility.

Because of its public health implications, the effect of quitting smoking on pancreas cancer risk is important to understand. Many studies have estimated risk for former and current smokers, but few studies have estimated risk by number of years quit smoking. Former smokers usually experience lower risk of pancreas cancer than current smokers (*26*). We observed ORs of 1.4 (95% CI = 1.1-1.9) for former smokers and 2.0 (95% CI = 1.5-2.6) for current smokers.

We also observed a negative trend in risk of pancreas cancer with increasing years of cessation of smoking. This finding is consistent with results of previous studies (*11,16,20,29*) that estimated risk by duration of abstinence. In the present study, smokers who quit for more than 10 years experienced about a 30% reduction in risk relative to current smokers; quitters of 10 years or less experienced no risk reduction. The delayed reduction in risk supports results of a large, population-based, case–control study conducted in Los Angeles (*11*) but contrasts with results of case–control studies in Toronto (*20*) and Washington state (*16*) that show a decline in risk within the first 10 years of smoking cessation. In view of the disparity in these findings, it is unclear whether cigarette smoking acts at a late stage in pancreatic carcinogenesis or whether the beneficial effect of quitting is simply due to a reduction in the total duration smoked.

Findings from five previous studies (*11,16,17,20,29*) indicate that risk of pancreas cancer among long-term quitters reverts to the level of risk experienced by nonsmokers after 10-20 years of abstinence. Results from four of these studies (*16,17,19,20*) were, however, based largely on interviews with next of kin of case patients, and the accuracy of recall of years quit by next of kin of subjects who quit smoking many years earlier is questionable. Our findings suggest that risk is greatly reduced among long-term quitters; those who quit for more than 20 years experienced a small, nonsignificant elevation in risk compared with that of nonsmokers (OR = 1.3; 95% CI = 0.8-1.9). There were too few smokers who quit for more than 30 years to determine whether risk eventually returns to the level of risk of nonsmokers or whether some irreversible damage to the pancreas occurs.

We also found that switching from filtered to nonfiltered cigarettes did not reduce risk of pancreas cancer. In fact, ORs by duration smoked filtered cigarettes were similar to ORs by duration smoked nonfiltered cigarettes. Only three previous studies (*17,19,20*) have examined risk by type of cigarette smoked. Our finding is consistent with that of the Toronto study (*20*), whereas studies conducted in Quebec (*19*) and The Netherlands (*17*), with the same study design as that of the Toronto study, found that risk associated with smoking nonfiltered cigarettes was higher than that associated with smoking filtered cigarettes. Given the sparsity of data regarding the effects of filtration, it is difficult to interpret these results. Because filtered cigarettes were smoked more recently than nonfiltered cigarettes, information on duration smoked nonfiltered cigarettes is more prone to misclassification than information on duration smoked filtered cigarettes, diluting the ORs for nonfiltered cigarettes more than those for filtered cigarettes. Case–control studies of other smoking-related sites, however, have detected reduced risks associated with filtered cigarettes, suggesting that misclassification may not be a serious problem. Alternatively, perhaps filtration offers little or no protection against the pancreatic carcinogen contained in cigarette smoke. Additional studies are needed to clarify the effects of filtration.

In summary, the relationship between cigarette smoking and risk of pancreas cancer is likely to be causal, despite the weakness of the dose–response data. Long-term smoking cessation clearly reduces risk, whereas switching from nonfiltered to filtered cigarettes may not be beneficial. Cigarette smoking appears to explain little of the excess risk of pancreas cancer experienced by blacks. From a public health perspective, we estimate that elimination of cigarette smoking would eventually prevent approximately 27% of pancreas cancer, saving 6750 lives in the United States each year.

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Notes

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